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Current Methods of Treatment for Hypertrophic Scars, keloids and future directions

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Abstract:

Hypertrophic scars and keloids arise due to dysregulated wound healing, often influenced by genetic predisposition, skin tension, infection, and anatomical site. Both conditions show increased fibroblast activity, overproduction of extracellular matrix proteins (especially type III collagen in hypertrophic scars and type I in keloids), and abnormal growth factor signaling (notably TGF-β). Treatment remains challenging due to high recurrence rates, particularly in keloids, necessitating multimodal and individualized strategies. The choice of therapy depends on scar type, size, location, symptoms, and patient characteristics.

Keywords: Hypertrophic scar; Keloid; Corticosteroid injection; Cryotherapy; Silicone gel; Radiotherapy; Laser therapy; Surgical excision; Pressure therapy; Intralesional therapy; Scar management.

Introduction:

Hypertrophic scars and keloids are pathological outcomes of abnormal wound healing characterized by excessive fibroblast activity and overproduction of collagen. These scars cause pain, pruritus, functional limitation, and psychological distress, making them clinically significant beyond cosmetic concerns **(1).**

Although they share similar histological features, hypertrophic scars typically remain within the wound boundaries and may regress spontaneously, while keloids extend beyond the original wound margin, show persistent growth, and are associated with a higher risk of recurrence **(2).**

The pathophysiology involves an imbalance in growth factor signaling, particularly upregulation of transforming growth factor-β (TGF-β), along with increased extracellular matrix deposition and reduced apoptosis of scar fibroblasts **(3).**

Treatment remains challenging due to high recurrence rates, especially in keloids. A multimodal approach combining preventive measures, pharmacological therapies, surgical techniques, and physical modalities is often required to improve outcomes **(4).**

Reducing tension on the wound with good surgical technique is an important aspect of prevention of hypertrophic scars during surgery. Patients who are known to form hypertrophic scars or keloids should avoid elective surgical procedures **(5).**

Preventative and non-invasive methods of treatment:

- **Occlusive dressings**

Silicone gel sheeting (SGS) is a commonly used occlusive dressing applied to reduce the risk of excessive scar formation. SGS is composed of a semi-occlusive silicone gel sheet combined with a durable silicone membrane. Though the prominent mechanism of action of these dressings is unclear, SGS is theorized to act via hydration and occlusion of the wound bed. Scar tissue has been shown to be more prone to transepidermal water loss, possibly reflecting decreased water barrier function of the stratum corneum. The SGS creates a moisture-retaining environment that prevents dehydration of the stratum corneum, which, in a

downstream manner, limits activation of fibroblasts and subsequent collagen production. SGS can reduce the incidence of hypertrophic scarring and reduce scar volume. The use of SGS requires high levels of patient adherence since protocols often require patients to wear the SGS upwards of 12 hours per day for at least 12 months. Efficacy of SGS has primarily been demonstrated when the dressing is used as a preventative measure rather than a method of treatment. The necessary continuous application of SGS in hotter climates might induce a level of humidity that facilitates the formation of bacterial abscesses **(6).**

- **Topical imiquimod**

Used successfully for the treatment of basal cell carcinoma and human papillomavirus-related warts, imiquimod 5% cream has shown promise as an adjuvant therapy for keloids after excision. Imiquimod is a Toll-like receptor 7 agonist that limits fibroblast production of collagen via increasing local concentrations of interferon alpha (IFN-α). IFN-α has been shown to decrease fibroblast activity in a dose-dependent manner, reduce glycosaminoglycan production, and increase collagenase levels. The reported recurrence rates of excised keloids with daily topical imiquimod 5% cream have ranged from 0 to 88.9 percent with a follow-up time of 20 to 24 weeks. The variability of the keloid recurrence rates with imiquimod therapy is likely related to skin tension at the operative site, with ear keloids having lower recurrence rates than shoulder, chest, and back keloids. Common side effects of imiquimod include hyperpigmentation, erythema, irritation, and secondary infections that typically resolve upon suspending therapy **(7).**

- **Angiotensin-converting enzyme inhibitor**

The renin-angiotensin-system has been shown to affect collagen production and wound healing. Although it is still under study, the local application of captopril cream (5%) and oral administration of enalapril improved keloids with no side effects. Therefore, these may be good treatment options for keloids **(8).**

- **Tacrolimus (FK-506)**

Tacrolimus is a calcineurin inhibitor and an immunosuppressive medication. When it was applied to keloid fibroblasts *in vitro*, it reduced their proliferation, migration, and collagen production. Clinically, tacrolimus is used as a topical medication for dermatological conditions such as atopic dermatitis. One patient using tacrolimus for treatment of atopic dermatitis reported that it also reduced keloid scarring. However, further research on the efficacy of tacrolimus is needed (**9).**

- **Laser Therapy**

Laser therapy is a widely used, energy-based treatment modality for skin resurfacing and other integumentary changes. Broadly speaking, lasers can be classified into two distinct categories: ablative or non-ablative. While non-ablative lasers leave the overlying epidermal layer intact, ablative lasers cause epidermal destruction and heating of the dermal layer. Both categories of laser, however, can be used in the treatment of keloids and HTS. Ablative lasers (eg, CO_2, erbium-doped yttrium aluminum garnet laser (Er:YAG) , and argon types) reduce scar volume by removing layers of scar tissue through interaction of the laser energy with the water in and on the skin. In contrast, non-ablative lasers (eg, neodymium-doped yttrium aluminum garnet (Nd:YAG), pulsed-dye laser (PDL), potassium titanyl phosphate (KTP), etc) target hemoglobin in red blood cells, leading to the destruction of microvasculature and ultimately hypoxia in the local tissue environment. This poor oxygenation leads to collagen remodeling and reduction. Such phenomena make laser therapy a promising therapeutic agent for keloids and HTS **(10).**

- **Non-Ablative Lasers**

Several different non-ablative laser modalities have demonstrated clinical efficacy with a favorable safety profile in patients of color. In 2013, Rossi et al established the success of a 300 microsecond Nd:YAG laser in the treatment of keloids in a sample (n=44) consisting of Fitzpatrick skin type (FSTs I–VI). Despite transient post-procedure erythema, Nd:YAG therapy demonstrated superior cosmesis, producing a substantial reduction in scar volume and vasculature in comparison to intralesional corticosteroid injection. Interestingly, all patients, including those of skin types IV–VI, did not exhibit dyschromia **(11).**

- **Ablative Lasers**

Lasers of the ablative type–namely CO_2 and erbium-based lasers–have been studied for their efficacy in treating HTS and keloids in FST IV–VI. Fully ablative laser technology for this scarring niche is sparse within the literature, perhaps due to its highly aggressive potential. A more recent alternative–the fractionally ablative laser–has perhaps received more research attention and been given its title as the "gold standard" due to its reduced traumatic impact and quicker healing time **(12).**

CO_2 laser therapy has boasted recent success in darker skin types. In 2015, a study by Azzam et al employed a split-scar treatment paradigm using fractional CO_2 laser monotherapy in a group with FSTs II–VI. Using Vancouver scar scale, the researchers established a significant decrease in scar severity on the treated scar portion, mainly attributable to increases in scar pliability, with little changes in pigmentation across all FSTs. Of relevance is the researchers' choice of pulse spacing; for patients with darker skin types, greater intervals were employed, suggesting the importance of tailoring laser parameters on an individual basis in order to combat the greater risks associated with laser therapy in this susceptible patient group. the significance of early therapeutic intervention when treating traumatic scars with fractional CO_2 laser in skin of color in order to improve scar pliability, height, and pigmentation **(13).**

Injections as a method of treatment:

- **Intralesional steroids**

As an accessible and efficacious keloid therapy, intralesional steroids continue to serve as a first-line treatment for many physicians. Typically, triamcinolone is injected at a concentration of either 2.5mg to 20mg for facial keloids or 20mg to 40mg for non-facial keloids. Corticosteroids act by suppressing wound inflammation mediators and fibroblast growth while increasing collagen degradation. Mechanisms by which triamcinolone alters fibroblast growth include inducing fibroblast hypoactivity by decreasing TGF-β expression and reducing fibroblast density by increasing fibroblast apoptosis. Intralesional triamcinolone as a monotherapy has been shown to reduce keloid recurrence to an average of 50 percent after surgical excision and to reduce scar volume. However, the therapeutic response rate of intralesional steroid therapy is highly variable. Potential side effects of corticosteroid injection include pain with injection, skin atrophy, alteration in skin pigmentation, and the formation of telangiectasias **(14).**

- **Botulinum toxin A**

Botulinum toxin type A (BoNT-A) has shown promising effects in improving scar appearance by modulating wound healing at both molecular and mechanical levels. BoNT-A reduces muscle tension around wounds, thereby decreasing mechanical stress that can exacerbate scar widening or hypertrophy. Additionally, BoNT-A has been found to downregulate inflammatory cytokines and fibroblast activity, resulting in reduced collagen deposition and fibroblast proliferation, which are key factors in pathological scarring. Clinical studies have reported that early post-surgical injection of BoNT-A can lead to thinner, softer, and more aesthetically favorable scars, particularly in high-tension facial areas **(15).**

The use of botulinum toxin A reduces tension on the wound edges by preventing muscle contraction during the healing process, thereby reducing scar formation. In fact, tension is one of the causes of keloid scars. Botulinum toxin A is given 4 to 7 days before surgery to reduce tension. Intralesional botulinum toxin injections resulted in improvement of keloids in a prospective, non-controlled study, and decreased keloid volume more effectively than intralesional corticosteroid injections. However, conflicting results have been reported for the therapeutic effects of botulinum toxin. Larger, randomized, controlled studies are needed to confirm its efficacy **(16).**

Combinatorial Treatments

Despite the demonstrated efficacy of energy- and non-energy-based modalities, monotherapeutic application appears to limit maximal results. Therefore, combining diverse therapies with varying operator techniques, treatment intervals, and sequences may enhance patient outcomes (**17**).

- **Multimodal Injection Therapy**

Injection therapy consisting of various corticosteroids and antineoplastic agents is a common combinatorial treatment. Triamcinilone acetonide (TAC) may be mixed with agents such as 5-FU and bleomycin. combinatorial intralesional injection of 5-FU and TAC (3:1) successfully reduced keloid volume, height, and penetration depth. Notable side effects included high rates of hyperpigmentation and telangiectasia. Similarly, the comparative efficacy of 585 nm PDL, TAC, 5-FU, TAC + 5-FU against a negative control. While results in scar volume reduction were similar between monotherapeutics and combinatorials, combinatorial administration of TAC and 5-FU eliminated hypopigmentation, atrophy, and telangiectasia that were associated with sole administration of TAC. Such favorable patient outcomes and minimal associated risk may soon qualify combined injection of TAC and 5-FU as a frontline therapy for skin of color **(18).**

- **Multimodal Laser Therapy**

Due to differential mechanisms, the employment of several types of lasers for the treatment of hypertrophic and keloid scars has gained increasing traction over monotherapeutic implementation. No side effects were observed following treatment; notably, patients pre-treated with a topical lightening agent and pressure therapy was employed following the laser procedure **(19).**

Invasive methods of treatment:

- **Surgery**

Surgical excision of keloids is a popular option and is recommended as the first-line treatment if disabling scar contracture is present. However, it should be used with caution since it often creates even larger lesions, and recurrence rates are high (45%–100%). Adjuvant measures, such as radiotherapy, interferon, bleomycin, cryotherapy, or corticosteroids, should be applied to avoid recurrence. For example, combining corticosteroid treatment with surgery reduced the recurrence rate to less than 50%, and the recurrence rate for surgery with adjuvant radiotherapy ranged from 0% to 8.6%. As a general rule, wound closure should be performed with minimal tension and sutures, and relaxed skin tension lines, leaving everted wound borders. In cases of scar contracture caused by excessive tension, Z-plasty, W-plasty, or various local flaps may be indicated **(20).**

- **Cryotherapy**

Cryotherapy leads to cellular injury and necrosis of keloid tissue. It can be administered by contact, spray, or intralesional injection. Intralesional cryotherapy concentrates the area of cold within the lesion, thereby minimally affecting the external skin; it is simple, can be applied to all types of scars, and is more effective than contact/spray treatment. Cryotherapy is applied monthly in multiple sessions, and the success rate after two sessions ranged from 30% to 75%. Cryotherapy, in combination with intralesional corticosteroid injection, has been the most popular traditional treatment for keloids. The most common side effect of cryotherapy is hypopigmentation, followed by blisters, local pain, and hyperpigmentation **(21).**

Future directions for scar management:

Gene Editing and Molecular Targeting

Following skin injuries, many genes are up- or downregulated to modify the wound environment **(Table 1)**. However, deregulated expression of the genes involved in this critical process can promote abnormal wound healing and scarring. Identification of these genes offers the opportunity to manage the different stages of wound healing and modulate fibrosis through gene therapy to convert scarring injuries into scar-free repaired wounds **(22).**

Table (1) Important genes during wound healing and scar formation (23).

Gene/factor	Role in		Effects
IL-8	Induction Inhibition	Inflammation; recruitment of immune cells and fibroblasts; hemostasis of epidermis; proliferation of keratinocytes; production of MMP-9 in keratinocytes; angiogenesis –	Pro-fibrotic
IL-1α	Induction Inhibition	Inflammation; activity of keratinocytes, fibroblasts, and endothelial cells; deposition of collagen Restoration of the skin architecture	Pro-fibrotic
IL-1β	Induction Inhibition	Expression of decorin; activity and homing of PBMC; function of CXCR4-CXCL 12 axis; proliferation of fibroblasts Restoration of the skin architecture	Pro-fibrotic
IL-6	Induction Inhibition	The pro-inflammatory function of immune cells; timely resolution of wound healing –	Pro-fibrotic

Gene transcripts are regulated based on the open or compact patterns of specific gene loci under a physiological or pathological condition. Such regulations can be conducted by the mechanisms encompassed in epigenetic knowledge. Epigenetic regulation has been recently investigated as the potential mechanism for changing the cell behavior and phenotype during wound healing and scar maintenance, thus promising novel targets for scar treatments **(24).**

Optimized wound healing requires the regulated patterns of DNA methylations and histone modifications, and epigenetic alterations may result in abnormal repair and scar formation. Hence, targeting epigenetic modifying enzymes provides the therapeutic opportunity to reverse these deleterious alterations. To date, several clinical trials have been performed based on the regulation of hypermethylation patterns of different genes, and several inhibitors of HDAC are already in clinical use **(25).**

Stem Cell Therapy

Mesenchymal stem cells MSCs are adult multipotent stromal cells that can be readily harvested from various sites such as bone marrow, adipose, and umbilical tissue, (MSCs) can be expanded ex vivo and cultured under specific conditions to promote particular cellular effects, due to their low immunogenicity, MSCs are frequently transplanted allogeneically for the treatment of inflammatory conditions. MSCs exert their anti-inflammatory and anti-fibrotic paracrine effects via the chemokines and microvesicles that they secrete. Whilst tissue native MSCs play a key role in potentiating this process, there is evidence to suggest that transplanted MSCs are instead able to attenuate inflammation and promote a return to homeostasis. MSCs may achieve this by mediating macrophage class switch from a proinflammatory M1 to anti-inflammatory M2 phenotype MSCs also have the potential to negatively modulate ECM deposition, possibly via promoting a T-cell response that results in the downregulation of TGF-β1, a key regulator of collagen synthesis **(26).**

They have aroused immense interests for clinical applications because of their easy availability and potential for recovering. Substantial animal and clinical studies have shown that MSCs can inhibit pathological fibrosis in many organs, such as the heart, lung, and kidney, and therefore can improve the prognosis of many diseases, such as liver injury, spinal cord injury, acute respiratory distress syndrome, blood disease, and critical limb ischemia. These provided a possibility of skin scar tissue repair affected by MSCs. Owing to their multifunctional roles, MSCs can migrate to the wound sites directionally. They formed a part of microenvironment, improved wound healing, and inhibited pathological skin scars. Among them, umbilical cord mesenchymal stem cells (UC-MSCs) are most easily accessible, with low immunogenicity, and can be expanded in vitro. UC-MSCs can be easily isolated and collected from the umbilical cord by using an accessible procedure. Previous researches have shown that MSCs can suppress proliferation and activation of keloid fibroblasts and inhibit extracellular matrix synthesis through a paracrine signaling mechanism and thus may be a novel topical agent for pathological skin scar treatment **(27).**

The clinical use of either embryonic stem cells or induced pluripotent stem cells remains limited because of cell regulations, ethical considerations, and the requirement for genetic manipulation. Adult autologous mesenchymal stem cells (MSCs) do not present these ethical issues and have been successfully explored in

clinical studies on fibrosis, particularly to treat liver cirrhosis, idiopathic pulmonary fibrosis, myocardial fibrosis, renal fibrosis and to repair pulmonary tissue that had been injured by thoracic irradiation. Among the different sources of MSCs, bone marrow has been the most commonly adopted, containing a population of MSCs called bone marrow stem cells (BMSCs). However, their use presents drawbacks: they are extracted by a painful process that may cause donor site morbidity in the patient, and because the retrieved marrow has less of them, ex vivo expansion is frequently required, Adipose tissue represents an attractive alternative source of MSCs as it is easily collected via a liposuction operation in large volumes and is abundant with MSCs called adipose-derived stem cells (ASCs) **(28).**

Moreover, the donor site treatment, which involves removing excess adipose tissue, is well tolerated and often welcomed by the patient. The ASCs therefore appear to be an ideal population of stem cells for practical regenerative medicine, given that they are plentiful, of autologous tissue origin and thus non-immunogenic, and are more easily available with minimal morbidity for patients. In addition to that, the ASCs seem to be more efficient in reducing skin fibrosis than the BMSCs **(29).**

Another interesting feature of ASC therapy is its immunomodulatory ability. By reducing the production of proinflammatory cytokines such as TNF-α and IFN-γ, adipose-derived stem cells (ASCs) establish a "virtuous circle" wherein fewer immune cells migrate to damaged tissues. This inhibition of the acute inflammatory reaction and cytokine production by ASCs contributes to a decrease in subsequent chronic inflammation and fibrosis. Moreover, the alleviation of tissue inflammation, enhancement of angiogenesis, and mitigation of oxidative stress further enhance their anti-fibrotic efficacy **(30).**

Laser-Assisted Drug Delivery

Laser-assisted drug delivery (LADD) is an evolving treatment modality. Ablative fractional lasers create vertical cone-shaped channels known as microablation zones (MAZ). Application of topical agents to MAZ allows for increased penetration of the stratum corneum and enhancing bioavailability of medications. The combination of ablative fractional laser treatment and topical medications is promising for the treatment of keloids **(31).**

The evidence suggests that LADD improves outcomes in hypertrophic scars and keloids. LADD is a more effective treatment modality than the topical application of agents in hypertrophic scars and equally effective as the intralesional injection of agents in keloids. There were few reports of adverse events. Evidence supports the use of LADD as an adjunct to non-surgical measures or a treatment modality to be used before more invasive measures such as surgical excision **(32).**

Artificial intelligence in scar treatment

Artificial intelligence (AI) and Machine learning (ML) have transformative potential in aesthetic medicine, offering improved diagnostic precision, enhanced patient outcomes, and cost reductions. Addressing limitations related to algorithm bias, regulatory oversight, and data quality is essential to fully realize the benefits of AI in clinical practice. The integration of AI and ML has revolutionized aesthetic medicine, enhancing the diagnosis, classification, and treatment of skin conditions. These technologies offer high precision, personalized care, and the potential to reduce human error. AI-based platforms facilitated personalized treatment plans, enhancing therapeutic outcomes while minimizing errors. The integration of AI reduced diagnostic time and lowered healthcare costs, demonstrating significant potential for improving patient care. However, challenges such as algorithmic bias, data privacy concerns, and the need for high-quality training datasets were highlighted **(33).**

References:

1- Ogawa, R. (2022). Keloid and hypertrophic scars are the result of chronic inflammation in the reticular dermis. International Journal of Molecular Sciences, 23(11), 6113. https://doi.org/10.3390/ijms18030606

2- Wong, T. S., Li, J. Z., Chen, S., Chan, J. Y. W., & Gao, W. (2021). The efficacy of intralesional triamcinolone acetonide for keloids and hypertrophic scars: A systematic review and meta-analysis. Frontiers in Medicine, 8, 642646. https://doi.org/10.3389/fmed 2021.645499

3- Arno, A. I., Gauglitz, G. G., Barret, J. P., & Jeschke, M. G. (2019). Up-to-date approach to manage keloids and hypertrophic scars: A useful guide. Burns, 40(7), 1255–1266. https://doi.org/10.1016/j.burns.2014.02.011

4- Lee, Y. I., Kim, J., Yang, C. E., Lee, S. Y., Lee, H. J., & Cho, Y. S. (2020). Current treatments for keloids: An update and review. Clinical and Experimental Otorhinolaryngology, 13(2), 176–182. https://doi.org/10.21053/ceo.2019.01818

5- Ogawa, R. (2022). The most current algorithms for the treatment and prevention of hypertrophic scars and keloids: a 2020 update of the algorithms published 10 years ago. Plastic and Reconstructive Surgery, 149(1), 79e-94e. https://doi.org/10.1097/PRS.0b013e3181c82dd5.

6- Knowles A, Glass DA 2nd. (2023). Keloids and hypertrophic scars. Dermatol Clin. ;41(3):509-517. https://doi.org/10.1016/j.det.2023.02.010.

7- Limandjaja, G. C., Niessen, F. B., Scheper, R. J., & Gibbs, S. (2020). The keloid disorder: heterogeneity, histopathology, mechanisms and models. Frontiers in Cell and Developmental Biology, 8, 360. https://doi.org/10.3389/fcell.2020.00360.

8- Grabowski, G., Pacana, M. J., & Chen, E. (2020). Keloid and hypertrophic scar formation, prevention, and management: standard review of abnormal scarring in orthopaedic surgery. JAAOS-Journal of the American Academy of Orthopaedic Surgeons, 28(10), e408–e414. https://doi.org/10.5435/JAAOS-D-19-00690.

9- Wu CS, Wu PH, Fang AH, Lan CC. 2012. FK506 inhibits the enhancing effects of transforming growth factor (TGF)-β1 on collagen expression and TGF-β/Smad signalling in keloid fibroblasts: implication for new therapeutic approach. Br J Dermatol.;167(3):532-541. https://doi.org/10.1111/j.1365-2133.2012.11023.x

10- Walsh, L. A., Wu, E., Pontes, D., Kwan, K. R., Poondru, S., Miller, C. H., & Kundu, R. V. (2023). Keloid treatments: an evidence-based systematic review of recent advances. Systematic Reviews, 12(1), 42. https://doi.org/10.1186/s13643-023-02192-7.

11- Yu, Y., Wu, H., Zhang, Q., Ogawa, R., & Fu, S. (2021). Emerging insights into the immunological aspects of keloids. The Journal of Dermatology, 48(12), 1817–1826. https://doi.org/10.1111/1346-8138.16149.

12- Lu, Y.-Y., Tu, H.-P., Wu, C.-H., Hong, C.-H., Yang, K.-C., Yang, H.-J., Chang, K.-L., & Lee, C.-H. (2021). Risk of cancer development in patients with keloids. Scientific Reports, 11(1), 9390. https://doi.org/10.1038/s41598-021-88789-1.

13- Memariani, H., Memariani, M., Moravvej, H., & Shahidi-Dadras, M. (2021). Emerging and novel therapies for keloids: A compendious review. Sultan Qaboos University Medical Journal, 21(1), e22. https://doi.org/10.18295/squmj.2021.21.01.004.

14- Nischwitz, S. P., Rauch, K., Luze, H., Hofmann, E., Draschl, A., Kotzbeck, P., & Kamolz, L. (2020). Evidence-based therapy in hypertrophic scars: An update of a systematic review. Wound Repair and Regeneration, 28(5), 656–665. https://doi.org/10.1111/wrr.12839.

15 Zhibo, X., & Miaobo, Z. (2008). Botulinum toxin type A affects cell cycle distribution of fibroblasts derived from hypertrophic scar. Journal of plastic, reconstructive & aesthetic surgery: JPRAS, 61(9), 1128-1129 . doi:10.1016/j.bjps.2008.05.003.

16- Elsaie, M. L. (2021). Update on management of keloid and hypertrophic scars: a systemic review. Journal of Cosmetic Dermatology, 20(9), 2729–2738. https://doi.org/10.1111/jocd.14310.

17- Liu, X., Chen, W., Zeng, Q., Ma, B., Li, Z., Meng, T., Chen, J., Yu, N., Zhou, Z., & Long, X. (2022). Single-cell RNA-sequencing reveals lineage-specific regulatory changes of fibroblasts and vascular endothelial cells in keloids. Journal of Investigative Dermatology, 142(1), 124–135. https://doi.org/10.1016/j.jid.2021.06.010.

18- Huang, C., Wu, Z., Du, Y., & Ogawa, R. (2020). The epidemiology of keloids. Textbook on Scar Management: State of the Art Management and Emerging Technologies, 29–35. https://doi.org/10.1007/978-3-030-44766-3_4.

19- Stevenson, A. W., Deng, Z., Allahham, A., Prêle, C. M., Wood, F. M., & Fear, M. W. (2021). The epigenetics

of keloids. Experimental Dermatology, 30(8), 1099–1114. https://doi.org/10.1111/exd.14414.

20- Anderson, J. B., Foglio, A., Harrant, A. B., Huang, C. A., Hultman, C. S., Mathes, D. W., & Chong, T. W. (2021). Scoping Review of Therapeutic Strategies for Keloids and Hypertrophic Scars. Plastic and reconstructive surgery. Global open, 9(3), e3469. https://doi.org/10.1097/GOX.0000000000003469.

21- Oliveira, G. V, Metsavaht, L. D., Kadunc, B. V, Jedwab, S. K. K., Bressan, M. S., Stolf, H. O., Castro, R. G., Bezerra, S., Calil, D. A., & Addor, F. A. Z. (2021). Treatment of keloids and hypertrophic scars. Position statement of the Brazilian expert group GREMCIQ. Journal of the European Academy of Dermatology and Venereology, 35(11), 2128–2142. https://doi.org/10.1111/jdv.17484.

22- Huang C, Liu L, You Z, Du Y, Ogawa R. (2018). Gene therapy in pathologic scars. In: Gene therapy in reconstructive and regenerative surgery. Springer; p. 37–48. https://doi.org/10.1007/978-3-319-78957-6_3.

23- Amjadian S, Moradi S, Mohammadi P. 2022. The Emerging Therapeutic Targets for Scar Management: Genetic and Epigenetic Landscapes. Skin Pharmacol Physiol. ;35(5):247-265. https://doi.org/10.1159/000524990.

24- Zhang, S., & Duan, E. (2015). Epigenetic regulations on skin wound healing: implications from current researches. Annals Of Translational Medicine, 3(16), 227. https://doi.org/10.3978/j.issn.2305-5839.2015.07.12.

25- Jones, L. R., Young, W., Divine, G., Datta, I., Chen, K. M., Ozog, D., & Worsham, M. J. (2015). Genome-wide scan for methylation profiles in keloids. Disease Markers, 2015(1), Article 943176. https://doi.org/10.1155/2015/943176.

26- Bojanic C, To K, Hatoum A, Shea J, Seah KTM, Khan W, Malata CM. (2021). Mesenchymal stem cell therapy in hypertrophic and keloid scars. Cell Tissue Res. 383(3):915-930. https://doi.org/10.1007/s00441-020-03361-z.

27- Fan, D., Zeng, M., & Xia, Q. (2020). Efficacy and safety of umbilical cord mesenchymal stem cells in treatment of cesarean section skin scars: A randomized clinical trial. Stem Cell Research & Therapy, 11(1), 244. https://doi.org/10.1186/s13287-020-01695-7.

28- Almadori A, Butler PEM. 2024. Scarring and skin fibrosis reversal with regenerative surgery and stem cell therapy. *Cells*;13(5):443. https://doi.org/10.3390/cells13050443.

29- Gimble, J.M.; Bunnell, B.A.; Chiu, E.S.; Guilak, F. (2011). Concise review: Adipose-derived stromal vascular fraction cells and stem cells: Let's not get lost in translation. Stem Cells, 29, 749–754. https://doi.org/10.1002/stem.629.

30- Mahmoud M, Abdel-Rasheed M., Galal E.R., El-Awady R.R. (2023). Factors Defining Human Adipose Stem/Stromal Cell Immunomodulation in Vitro. Stem Cell Rev. Rep. 20:175–205. https://doi.org/10.1007/s12015-023-10654-7.

31- Truong, Kelvin, Ines Prasidha, and Tevi Wain. (2022). "A systematic review of randomised controlled trials investigating laser assisted drug delivery for the treatment of keloid and hypertrophic scars." Lasers in medical science 37.1; 47-59. https://doi.org/10.1007/s10103-021-03296-z.

32- Bernabe RM, Choe D, Calero T, Lin J, Pham C, Dang J, Madrigal P, Yenikomshian HA, Gillenwater TJ. (2024). Laser-Assisted Drug Delivery in the Treatment of Hypertrophic Scars and Keloids: A Systematic Review. J Burn Care Res. 6;45(3):590-600. https://doi.org/10.1093/jbcr/irae023.

33-Lee, A. K. W., Chan, L. K. W., Lee, C. H., Bohórquez, J., Haykal, D., et al. (2025). Artificial Intelligence Application in Diagnosing, Classifying, Localizing, Detecting and Estimating the Severity of Skin Condition in Aesthetic Medicine: A Review. Dermatological Reviews, 6(1), e70015. https://doi.org/10.1002/der2.70015.